Sone H, Tanaka S, Iimuro S, Oida K, Yamasaki Y, Ishibashi S, Oikawa S, Katayama S, Ito H, Ohashi Y, Akanuma Y, Yamada N, JDCS Group.	Waist circumference as a cardiovascular and metabolic risk in Japanese patients with type 2 diabetes.	*Obesity*	17:	585-92,	2009.
Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Sato M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H.	Influence of Fat and Carbohydrate Proportions on the Metabolic Profile in Patients with Type 2 Diabetes: A Meta-analysis.	*Diabetes Care*	32:	959-965,	2009
Sone H, Yoshimura Y, Tanaka S, Iimuro S, Ohashi Y, Ito H, Seino H, Ishibashi S, Akanuma Y, Yamada N; for the Japan Diabetes Complications Study (JDCS) Group.	Cross-sectional association between BMI, glycemic control and energy intake in Japanese patients with type 2 diabetes Analysis from the Japan Diabetes Complications Study.	*Diabetes Res Clin Pract*	77 Suppl1:	S23-29,	2007.

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ARTICLE

Long-term lifestyle intervention lowers the incidence of stroke in Japanese patients with type 2 diabetes: a nationwide multicentre randomised controlled trial (the Japan Diabetes Complications Study)

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Abstract
Aims/hypothesis The aim of the study was to clarify whether a therapeutic intervention focused on lifestyle modification affected the incidence of vascular complications in patients with established diabetes.
Methods A total of 2,033 eligible Japanese men and women aged 40–70 years with type 2 diabetes from 59 institutes were randomised to a conventional treatment group (CON), which continued to receive the usual care, and a lifestyle intervention group (INT), which received education on lifestyle modification regarding dietary habits, physical activities and adherence to treatment by telephone counselling and at each outpatient clinic visit, in addition to the usual care. Randomisation and open-label allocation were done by a central computer system. Primary analysis regarding measurements of control status and occurrence of macro- and microvascular complications was based on 1,304 participants followed for an 8 year period.
Results Although status of control of most classic cardiovascular risk factors, including body weight, glycaemia, serum lipids and BP, did not differ between groups during

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the study period, the incidence of stroke in the INT group (5.48/1,000 patient-years) was significantly lower than in the CON group (9.52/1,000 patient-years) by Kaplan–Meier analysis (p=0.02 by logrank test) and by multivariate Cox analysis (HR 0.62, 95% CI 0.39–0.98, p=0.04). The incidence of CHD, retinopathy and nephropathy did not differ significantly between groups. Lipoprotein(a) was another significant independent risk factor for stroke.
Conclusions/interpretation These findings suggest that lifestyle modification had limited effects on most typical control variables, but did have a significant effect on stroke incidence in patients with established type 2 diabetes.

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Keywords Complications · Lifestyle intervention · Patient education · Stroke

Abbreviations

CON	Conventional treatment group
CVD	Cardiovascular disease
IGT	Impaired glucose tolerance
INT	Lifestyle intervention group
JDCS	The Japan Diabetes Complications Study

Introduction

Lifestyle management through patient education plays a crucial role in prevention and care of diabetes. It is well established that lifestyle interventions, including diet and/or exercise, can prevent type 2 diabetes [1–6] as well as ameliorate glycaemia and other risk factors for complications [7–12] in patients with established diabetes. Recent reports of two studies that examined the effect of a lifestyle intervention on individuals with impaired glucose tolerance (IGT) over a long-term follow-up period (the China Da Qing Diabetes Prevention Study [13] and the Finnish Diabetes Prevention Study [14]), failed to show significant effects on cardiovascular disease (CVD) events or mortality. However, it is not known whether an intervention mainly focusing on lifestyle modification through patient education could prevent the occurrence of complications in patients with established diabetes, although there have been a few studies [15, 16] on lifestyle modification in combination with pharmacotherapy for hyperglycaemia, hypertension and dyslipidaemia in patients with type 2 diabetes.

The Japan Diabetes Complications Study (JDCS), a nationwide randomised controlled study of Japanese patients with type 2 diabetes, was designed to clarify whether a long-term therapeutic intervention mainly focused on lifestyle education has an effect on the incidence of diabetic macro- and microvascular complication events in patients with established type 2 diabetes (see Electronic supplementary material for members of JDCS). Another aim of this study was to clarify pathophysiological characteristics in East Asian patients with type 2 diabetes [17–20]. We previously published a 3 year interim report [21] showing significant but only limited improvement in glycaemia and no improvement in body weight, BP and serum lipids as a result of lifestyle modifications in patients with type 2 diabetes. This result was quite consistent with other subsequent studies with similar observation periods [8, 11, 22, 23]. The present report shows results after 8 years of an investigation that focused on the incidence of macro- and microvascular complications of diabetes.

Methods

Recruitment of patients Participants in the study were previously diagnosed patients with type 2 diabetes aged 40–70 years whose HbA_{1c} levels were ≥6.5%. From outpatient clinics in 59 university and general hospitals nationwide that specialise in diabetes care, a total of 2,205 patients (mean age 58.6 years; 47% women) were initially registered from January 1995 to March 1996. Excluded were patients with a history of angina pectoris, myocardial infarction, stroke, peripheral arterial disease, familial hypercholesterolaemia, type III hyperlipidaemia, non-diabetic nephropathy, nephrotic syndrome, pre-proliferative and proliferative retinopathy, intra-ocular surgeries, serum creatinine levels >120 μmol/l, and mean values of two spot urine examinations for an albumin excretion rate of <150 mg/g creatinine. Diabetes mellitus and IGT were diagnosed according to the Report of the Committee of the Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus, which is almost identical in terms of cut-off values for glucose levels to those of the WHO. The protocol for the study, which is in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical/Epidemiological Studies of the Japanese Ministry of Health, Labour and Welfare, received ethical

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approval from the institutional review boards of all of the participating institutes (RCT registration number was C000000222 in www.umin.ac.jp). Written informed consent was obtained from all patients enrolled.

Allocation of patients Before April 1996, when the intervention began, patients who did not meet the eligibility criteria were excluded. Finally, a total of 2,033 patients aged 58.5±6.9 years and who had diabetes for a duration of 10.9±7.2 years (both mean ± SD) were included from the present analysis. Figure 1 is a flow diagram of the JDCS. Patients were allocated randomly into either a lifestyle intervention (INT) group or a conventional treatment (CON) group. Randomisation and all analyses were done by a central computer at our database centre. This study was open-labelled and the interventions for the INT group were continued until March 2003.

Lifestyle intervention As basal therapeutic management of all patients in both the CON and INT groups, regular specialists' care was provided throughout the study period and patients were treated as they were before the study started. This included dietary advice by an administrative dietitian, using the 'Food Exchange Lists Dietary Guidance for Persons with Diabetes' [24].

In addition to this routine conventional treatment, education of patients in the INT group was given through individual counselling on dietary habits, physical activities and adherence to treatment, including taking medicine properly. Counselling was provided by physicians, nurses, dietitians and other co-medical staff during each outpatient clinic visit. Patients in the INT group had a typically 5–10 min longer interview than the patients in the CON group at each clinic visit for a discussion on possible causes of any changes in HbA_{1c} levels, weight and other control variables from the previous visit, with emphasis on lifestyle changes. For example, when it was revealed that control of glycaemic and other variables had worsened, that dietary intake, including quantity and content, and alcohol intake had changed, that patterns of physical activity had changed or that patients tended to forget to take their medicine, possible strategies for improving lifestyle and habits were discussed. Furthermore, patients in the INT group also received additional advice regarding one or two particular topic(s) at each visit and were given educational material consisting of 23 brochures that discussed various aspects of diabetes care with an emphasis on the importance of lifestyle and behavioural changes such as 'Why am I obese even if I do not eat so much?', 'Tips for continuing exercise', 'What kinds of stress affect the control of diabetes' or 'Is your triglyceride level OK?'.

Patients in the INT group also received 15 min telephone counselling sessions at least once every 2 weeks by nurses, dietitians and psychotherapists who were trained in diabetes education. These telephone sessions were performed based on a structured and uniform format. Additional counselling sessions were encouraged at any convenient time, depending on the needs of patients in the INT group. A diary to record the progress of laboratory and other data was distributed to the INT patients to provide better feedback on therapeutic results. A pedometer was also distributed to INT patients for objective exercise assessment.

Goals were set for patients in the INT group and their physicians: i.e. HbA_{1c} level <6.5%; BMI <22 kg/m^2; BP <140/85 mmHg; serum cholesterol level <5.72 mmol/l; serum triacylglycerol level <1.65 mmol/l; serum HDL-cholesterol >1.04 mmol/l; WHR <0.9 for men and <0.8 for women; smoking cessation; and abstinence from alcohol. Goals regarding BP and serum cholesterol levels were updated in accord with the revision of guidelines made by the Japan Diabetes Society, which were <130/80 mmHg and <5.17 mmol/l, respectively.

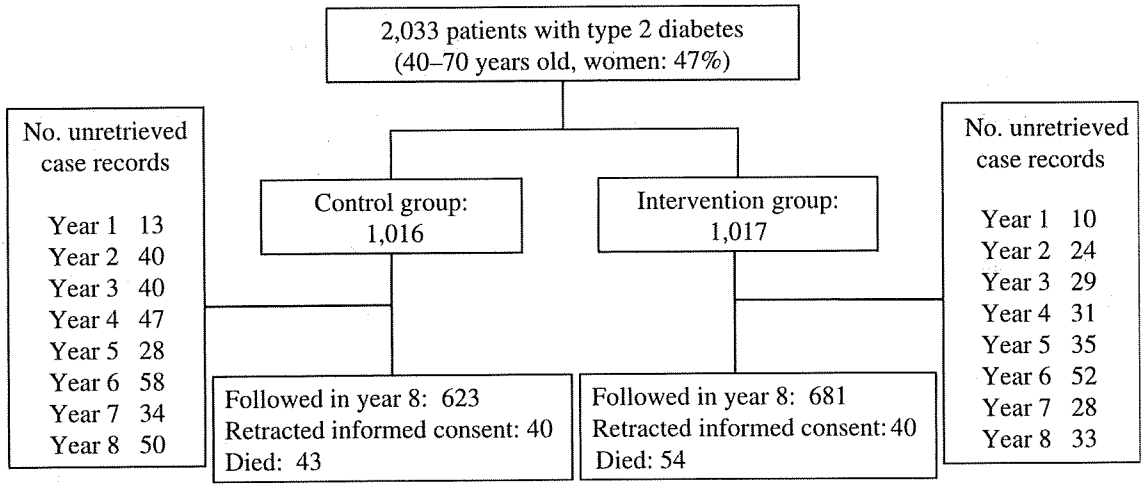

Fig. 1 Flow diagram of the JDCS

During the study period, patients in the INT group with poor control (HbA_{1c} >8.0%, serum total cholesterol level >5.72 mmol/l, serum triacylglycerol level >1.65 mmol/l or BMI >22 kg/m^2) were identified and sent additional educational material. At the same time, their physicians were encouraged to strengthen the intervention through increasing time for education by telephone or at clinic visits or recommending hospital admissions for education. Changes in medication including insulin and oral antihypertension/dyslipidaemia agents were not restricted in either group and were made based on therapeutic necessity.

Assessment of lifestyle Extensive lifestyle surveys were performed at baseline and 5 years after the start of the intervention in both groups. We used detailed questionnaires for patients to determine dietary (including alcohol drinking) content, amount of exercise and smoking rate. The dietary survey comprised food records and a food frequency questionnaire, results of which were analysed by an administrative dietitian using standardised software for population-based surveys and nutrition counselling in Japan (EIYO-KUN v.4.5, manufactured at Shikoku University Nutrition Database) [25] based on the Standard Tables of Food Composition in Japan [26] edited by the Japanese Ministry of Education, Culture, Sports, Science and Technology. Physical activity was determined by a questionnaire that inquired about types of exercise (walking, jogging, tennis, etc) and average time (min) spent exercising per day at baseline and the Baecke's Total Physical Activity Index [27] at the fifth year.

Clinical and laboratory measurements Mean values of at least two measurements each year were obtained for the following variables: HbA_{1c}, fasting plasma glucose/insulin/C-peptide, serum lipids/creatinine/urea nitrogen, and urine analysis. All other measurements including those for body weight, BP and WHR and a neurological/ophthalmological examination were done at least once yearly, with a mean value obtained if measurements were done twice a year. HbA_{1c} assays were standardised by the Laboratory Test Committee of the Japan Diabetes Society, with 5.8% as the upper normal limit. All other laboratory tests were done by standard methods in each clinic. Electrocardiograms and chest x-rays were performed annually. Patients were assessed yearly after the baseline evaluation.

Endpoints of the study Primary outcomes of the study were development and progression of microangiopathy and occurrence of macrovascular complication events. Microangiopathy endpoints consisted of those related to retinopathies and nephropathies. Retinopathy was evaluated by qualified ophthalmologists using the following classification designed for this research: Stage 0, no retinopathy; Stage 1, haemorrhage and hard exudates; Stage 2, soft exudates; Stage 3, intraretinal microvascular abnormalities and venous changes including beading, loop and duplication; Stage 4, new vessels, vitreous haemorrhage, fibrous proliferation and retinal detachment. The retinopathy endpoint was (1) development of retinopathy (from Stage 0 to any other stage confirmed in two continuous years), and (2) progression from Stage 1 to Stage 3 or 4. The nephropathy endpoint was defined as development of overt nephropathy (spot urinary albumin excretion >300 mg/g creatinine in two consecutive samples).

Macroangiopathy endpoints included the occurrence of definite CHD (angina pectoris or myocardial infarction) or stroke. Diagnosis of angina pectoris and myocardial infarction was according to criteria defined by the WHO/MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) project and diagnosis of stroke was according to guidelines defined by the Ministry of Health, Labour and Welfare of Japan [21]. Information regarding primary outcome and other clinical variables for each patient was collected through an annual report from each physician. Adjudication of endpoints was made by central committees comprising experts in each complication based on additional data such as CT or MRI of the brain or sequential changes in electrocardiograms.

Statistical analysis The sample size required to compare the net change in HbA_{1c} level (level at the third year point minus the baseline level) between the INT and CON groups is based on a consideration of power. It is assumed that the type I error (α) is 0.05 and the type II error (β) is 0.1; therefore, in order to detect a difference of 0.2 in net change in HbA_{1c} level, with an SD of 1.0 among patients, a total sample size of 1,025 is required. In addition, if allowance is made for an up to 20% dropout rate, for 20% of the INT group being unable to complete the intervention and for 10% of the CON group to change treatment method within the follow-up period, the required sample size increases to 2,616. Thus, in terms of the feasibility of the study, it was necessary to recruit more than 2,000 patients. All statistical analyses and data management were conducted at a central data centre. The Wilcoxon's rank sum test, Fisher's exact test and Mantel's test were used for comparison of numerical and categorical variables between groups.

The study endpoints were analysed as time-to-event variables, i.e. clinical data on patients who were lost during follow-up were used for the period for which they could be followed. Survival curves for the diabetic complications were estimated by the Kaplan–Meier method, and the logrank test was also conducted. Cox regression analysis was used to calculate the unadjusted and adjusted HRs and 95% CIs for group and risk factors. In multivariate Cox analysis, all significant variables selected for the univariate

analysis were used with the criterion of $p<0.1$. All values are presented as means ± SD unless otherwise stated. All p values are two-sided and the significance level is 0.05. All statistical analyses were conducted using SAS packages ver. 9.1 (SAS Institute, Cary, NC, USA).

Results

Clinical variables and their changes Clinical characteristics of the patients at baseline and at the fourth and eighth year after the start of the study are shown in Table 1. There were no differences in most variables between the two groups except for the triacylglycerol level, which was slightly but significantly lower in the INT group at the eighth year. Proportions of patients using agents for hyperglycaemia, including insulin, hypertension and dyslipidaemia and anti-platelet agents did not differ significantly between groups. Frequency of clinic visits also did not differ between groups. Proportions of patients who satisfied all or each of the components of the therapeutic goals did not differ between groups at either the fourth or eighth year. Median follow-up time was 7.8 years.

Of the eligible patients, 73% were followed into the eighth year. The dropout rate, which was defined as the proportion of patients who were lost-to-follow up until the eighth year, in the INT group (24%) was significantly lower than in the CON group (31%). Significant differences in baseline characteristics between patients who completed (i.e. were followed until the end of the observation period) and did not complete (i.e. dropped out during the observation period) follow-up were only found in the proportion of patients on insulin (22% completed vs 18% did not complete, $p=0.03$), in current smokers (20% completed vs 7.5% did not complete, $p=0.01$) and amount of daily exercise (590 kJ/day completed vs 351 kJ/day did not complete, $p<0.0001$).

Effects of lifestyle modification There were no differences in energy or fat intake between groups in either the fifth or the eighth year of the study (Table 1). Physical activity as determined by the Baecke's Total Physical Activity Index [27] after 5 years of intervention was significantly higher in the INT group than in the CON group, with the difference in the total score being derived from the Sports Index (4.1 in the INT group vs 3.7 in the CON group, $p=0.028$), but not Work or Leisure Indices. The proportion of current smokers in both groups decreased from 28% to 23%, with no significance between groups.

Primary endpoint analysis During the study period, 345 retinopathy, 74 nephropathy, 115 CHD and 90 stroke events occurred. Among all CHD events, 60% ($n=69$) were angina pectoris and 40% ($n=46$) were myocardial infarction, and among all stroke events, 83% ($n=75$) were brain infarction, 9% ($n=8$) were brain haemorrhage and 8% ($n=7$) were transient ischaemic attack. Kaplan–Meier curves for macro- and microvascular endpoints are shown in Fig. 2, which demonstrates that the incidence of stroke in the INT group was significantly lower than that in the CON group.

Risk factors for stroke analysed by univariate and multivariate Cox proportional hazard models are shown in Table 2, and belonging to the INT group was associated with an approximately 40% significant risk reduction for stroke by both univariate and multivariate analyses when all significant variables determined by univariate analysis were included. Systolic BP and lipoprotein(a) were also significant factors that remained in multivariate analysis. Despite this, absolute values for BP and lipoprotein(a) did not differ significantly between groups. Even when myocardial infarction (including asymptomatic) or brain infarction was used as an endpoint instead of CHD or stroke, respectively, the above results were not changed (data not shown).

No group differences were found in the occurrence of CHD, development of retinopathy (35.7/1,000 patient-years in the CON group vs 39.0 in the INT group), progression of retinopathy (6.5/1,000 patient-years in the CON group vs 10.0 in the INT group) or development of nephropathy (6.7/1,000 patient-years in the CON group vs 6.7 in the INT group).

Discussion

Although lifestyle interventions in patients with type 2 diabetes have traditionally focused almost exclusively on weight loss, control of glycaemia and other major cardiovascular risk factors should also be considered simultaneously for the prevention of complications [28, 29]. Systematic reviews and meta-analyses have revealed clinically significant but considerably mild effects of lifestyle interventions on glycaemic control, that is about a 0.5% reduction in HbA_{1c} with some variations in HbA_{1c} levels depending on the study and its design [8, 11, 22, 23]. In the Steno-2 study [16], the difference in mean HbA_{1c} levels between the conventional and intensive therapy groups after 7.8 years of follow-up was 1.1%, with a marked reduction in many diabetic complications. This was accomplished through not only behavioural modification but also pharmacological therapy for control of glycaemia, BP and serum lipid levels. HbA_{1c} levels were not reported in previous studies that examined the effects of a lifestyle intervention on cardiovascular events in individuals with IGT [13, 14]. The current study, together with our previous interim report [21], added the information that a lifestyle intervention produced significant but small and temporal

Table 1 Patient characteristics at baseline and 4 and 8 years after start of the intervention in each group

Variable	Baseline		4 years after start of intervention			8 years after start of intervention		
	CON	INT	CON	INT	*p* value[b]	CON	INT	*p* value[b]
No. patients (men/women)	1,016 (538/478)	1,017 (549/468)	850 (437/413)	882 (468/414)		630 (326/304)	689 (369/320)	
Age (years)	58.6±7.0	58.5±6.9	62.8±6.8	62.4±6.9	0.22	66.7±6.8	66.3±6.8	0.28
BMI (kg/m^2)	23.0±2.9	23.1±3.1	23.0±3.0	23.0±3.1	0.96	23.1±3.1	23.0±3.2	0.50
Blood pressure (mmHg)	132±16/77±10	132±16/77±10	132±15/75±9	133±16/76±9	0.23/0.33	132±16/74±10	133±16/74±10	0.17/0.99
Fasting plasma glucose (mmol/l)	9.0±2.4	8.8±2.4	8.9±2.6	8.8±2.5	0.14	8.7±2.6	8.6±2.4	0.90
HbA_{1c} (%)	7.9±1.3	7.8±1.2	7.7±1.2	7.6±1.2	0.10	7.6±1.2	7.7±1.2	0.47
Serum total cholesterol (mmol/l)	5.21±0.92	5.21±0.89	5.20±0.86	5.17±0.86	0.44	5.20±0.80	5.20±0.80	0.32
Serum triacylglycerol (mmol/l)[a]	1.17 (0.85)	1.15 (0.84)	1.14 (0.75)	1.14 (0.78)	0.55	1.19 (0.81)	1.09 (0.76)	0.049
Serum HDL-cholesterol (mmol/l)	1.42±0.46	1.41±0.42	1.50±0.42	1.49±0.44	0.39	1.50±0.40	1.50±0.40	0.88
Serum lipoprotein(a) (mmol/l)[a]	0.82 (1.03)	0.84 (1.10)	0.85 (1.02)	0.83 (1.00)	0.53	0.72 (0.86)	0.75 (1.10)	0.53
Therapeutic measures								
Diabetes								
Diet only (%)	19.1	19.4	7.2	8.5	0.32	3.7	3.5	0.88
Insulin (%)	21.6	20.2	35.2	32.3	0.22	44.3	42.2	0.45
Sulfonylureas (%)	56.7	57.9	62.1	62.7	0.80	56.4	60.5	0.15
α-Glucosidase inhibitors (%)	19.6	20.5	28.9	31.8	0.21	28.2	30.7	0.35
Biguanides (%)	5.4	4.3	15.6	16.6	0.60	31.3	33.6	0.39
Insulin sensitiser (%)	2.0	2.7	8.2	8.6	0.73	8.5	9.3	0.62
Others								
Antihypertensive agents (%)	26.8	27.7	35.5	36.2	0.76	47.8	47.4	0.91
Agents for hyperlipidaemia (%)	26.0	24.5	33.0	32.1	0.72	39.3	37.9	0.64
Diet								
Energy intake (kJ/day)[a]	7,101 (2,258)	7,092 (2,245)	6,891 (2,196)[d]	6,929 (2,062)[d]	0.60[d]	ND	ND	
Fat intake (g/day)[a]	52 (21)	51 (22)	48 (22)[d]	50 (22)[d]	0.30[d]	ND	ND	
Exercise (kJ/day for baseline and Baecke's score for the fourth year)[a]	502 (1,083)	565 (1,142)	9.3 (17.6)[d]	9.9 (17.5)[d]	0.037[d]	ND	ND	
Current/past smoker (%)	29/22	27/25	24/26[d]	21/30[d]	0.21[d]	ND	ND	
Alcohol intake per day: never, one drink or less, more than one drink[c] (%)	64/30/6	62/30/7	65/31/5[d]	60/33/7[d]	0.11[d]	ND	ND	

Means ± SD, unless otherwise stated

[a] Median (interquartile range)

[b] *p* values CON vs INT groups (Fisher's exact test for therapeutic measures, Mantel's test for smoking status and alcohol intake and Wilcoxon's rank sum test for other variables)

[c] 'One drink' is equivalent to 12.6 g of ethanol based on the US Department of Agriculture definition

[d] After 5 years

ND, not done

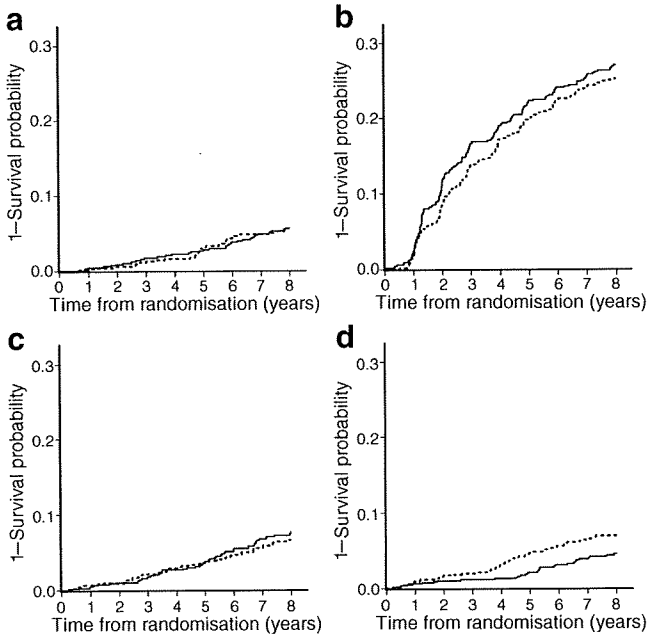

Fig. 2 Kaplan–Meier curves for each complication. **a** Nephropathy, $p=1.00$. **b** Retinopathy, $p=0.43$. **c** CHD, $p=0.40$. **d** Stroke, $p=0.02$. p values by logrank test. Dotted curves, CON; solid curves, INT

improvement in glycaemic control and only minimal changes in other known risk factors for diabetic complications, indicating the difficulty in changing the lifestyle of patients with long-term diabetes.

One possible reason for these limited effects on lifestyle and risk factors was that the intensity of our lifestyle intervention, which consisted only of education, was considerably lower than that in other studies [3, 15]. The rationale for this strategy was to determine if an intervention that is practicable to apply in the clinical 'real-world' setting with limited resources would be effective. Our results showed only very limited changes in actual lifestyle as well as major risk factors.

Another reason for the limited effects is that, in our study, even patients in the CON group received routine lifestyle education by diabetes specialists, which is an inevitable part of the usual care of persons with diabetes. Consequently, the effects of the lifestyle intervention was somewhat 'diluted'. The sequential increase in mean weight seen in the UK Prospective Diabetes Study (UKPDS) [30] was not observed in this study even in the CON group, indicating some effect of even routine lifestyle education. Also, perhaps if individualised goals with designated per cent changes for each patient in the INT group had been established instead of uniform goals for the entire group, results for the INT group might have been different. Further examination of results might have indicated which subgroups within the INT group would be most likely to benefit from such an intervention, which would be helpful in planning future interventions.

Nevertheless, we found a significant reduced risk for stroke in patients in the INT group compared with those in the CON group regardless of the lack of significant differences in most known cardiovascular risk factors. The mechanism of this apparent contradictory result is yet to be determined but it should be interpreted with care, especially since BP, which is a major risk factor for stroke, did not differ significantly between groups throughout the study period. Multifactorial or combined effects of lifestyle education/behaviours beyond individual factors [31] might have existed but can only be speculated upon. At the same time, the slight but significant differences in HbA_{1c} in the first 3 years, which was reported previously [21], but that disappeared thereafter, could enhance the effects since past interventions to lower HbA_{1c} reportedly have had a very long-term effect (i.e. 'metabolic memory' or 'legacy effect') [32, 33].

Other speculations for the apparent contradictory result include possible improvement in factors that were not determined in this study, such as postprandial glycaemia/lipaemia, BP at home or psychological factors (stress,

Table 2 Risk factors for stroke analysed by Cox univariate and multivariate models

Variable	HR (95% CI)	p value
Univariate analysis		
Sex (women vs men)	0.65 (0.42–1.00)	0.05
Age (per 10 years)	1.53 (1.11–2.13)	0.01
Diabetes duration (per 10 years)	0.95 (0.70–1.28)	0.72
HbA_{1c} (per 1%)	1.12 (0.97–1.30)	0.13
BMI (per 1 kg/m^2)	1.05 (0.98–1.12)	0.18
Waist circumference (per 10 cm)	1.38 (1.09–1.74)	0.01
Systolic BP (per 10 mmHg)	1.22 (1.07–1.38)	<0.01
Diastolic BP (per 10 mmHg)	1.18 (0.96–1.45)	0.12
LDL-cholesterol (per 1 mmol/l)	1.06 (0.82–1.37)	0.66
HDL-cholesterol (per 1 mmol/l)	0.62 (0.37–1.06)	0.08
Triacylglycerol (per 1 mmol/l)	1.16 (0.96–1.41)	0.14
Lipoprotein(a) (per 1 μmol/l)	1.17 (1.04–1.31)	0.01
Current smoker (yes vs no)	1.22 (0.95–1.56)	0.13
Alcohol intake (per 10 g ethanol)	1.06 (0.97–1.16)	0.23
Exercise amount (per 418 kJ)	1.01 (0.93–1.09)	0.80
INT group (vs CON group)	0.61 (0.39–0.93)	0.02
Multivariate analysis		
Sex (women vs men)	0.68 (0.42–1.11)	0.12
Age (per 10 years)	1.42 (0.99–2.04)	0.06
Systolic BP (per 10 mmHg)	1.22 (1.05–1.40)	0.01
Lipoprotein(a) (per 1 μmol/l)	1.16 (1.03–1.31)	0.01
INT group (vs CON group)	0.62 (0.39–0.98)	0.04

All significant variables selected for the univariate analysis with the criterion of a $p<0.1$ were used in the multivariate analysis

motivation or quality of life) [34], which could be ameliorated in the INT group rather than in the CON group. For example, Roumen et al. [35] recently reported that a lifestyle intervention successfully improved post-prandial glucose levels in IGT patients. Changes in diet might also be effective, such as an increase in fruit intake, which is reportedly associated with reduced CVD mortality [36]. The reasons that only stroke, but not CHD or other complications, was found to be responsive to our intervention are speculated to include the following: (1) stroke is more frequent than CHD in Japan compared with other parts of the world, and (2) the independent risk factor for stroke was only systolic BP and lipoprotein(a), and so there would be room for other undetermined risk factors to work.

Telephone counselling in patients with chronic disease was shown to be associated with a 41% significant reduction in the risk of death [37]. However, attempts to use telephone calls in diabetes care have resulted in relatively mild [38, 39] or no additional [40] effects on control variables or improved quality of life [41] or patient satisfaction [39]. However, its effects on complication events have not been determined previously. Current results suggested that the telephone intervention could have contributed to a reduction in complication events. Further investigation is required to clarify whether telephone counselling alone is effective in improving the occurrence of complication events or death.

Lipoprotein(a), primarily a genetically determined risk factor for atherothrombogenesis, was found to be one significant predictor of stroke in our analysis. It has been reported as a predictor of deterioration of renal function [42], peripheral arterial disease [43], CVD [44] including CHD [45], and cardiovascular mortality [46] in patients with type 2 diabetes and a predictor of CVD [47] in patients with type 1 diabetes. It is of interest that the serum level of lipoprotein(a), which is known to be less affected by lifestyle or medication than other cardiovascular risk factors [48], was also a significant factor independent from lifestyle in our cohort.

The strengths of our study are that (1) it is the first intervention study mainly focused on the effects of lifestyle education on diabetic vascular complications, and (2) follow-up was done by diabetes specialists, ensuring that the quality of data was relatively high. Nevertheless, we acknowledge that the study had certain limitations. First, our participants were hospital-based patients with diabetes of a relatively long duration. Therefore, we cannot make inferences beyond a similar group. Second, only Asian diabetic patients were involved and they are different from other ethnic groups in terms of degree of obesity [49]. Third, we had a low follow-up rate, since the study was done mainly in large hospitals in urban areas where patients move quite frequently. However, it is less likely that this could be a cause of an inter-group difference in stroke incidence since significant differences in the incidence of stroke between groups could already be seen 4–5 years after the intervention began, when the follow-up rates of the two groups were not significantly different.

A therapeutic intervention mainly focused on lifestyle changes produced a significantly reduced risk of stroke in Japanese patients with type 2 diabetes independently of known classic risk factors. The detailed mechanisms for this effect should be investigated in the future.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

References

1. Pan XR, Li GW, Hu YH et al (1997) Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 20:537–544
2. Tuomilehto J, Lindstrom J, Eriksson JG et al (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 344:1343–1350
3. Knowler WC, Barrett-Connor E, Fowler SE et al (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393–403
4. Kosaka K, Noda M, Kuzuya T (2005) Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res Clin Pract 67:152–162
5. Lindstrom J, Ilanne-Parikka P, Peltonen M et al (2006) Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 368:1673–1679
6. Gillies CL, Abrams KR, Lambert PC et al (2007) Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 334:299–302
7. Conn VS, Hafdahl AR, Mehr DR, LeMaster JW, Brown SA, Nielsen PJ (2007) Metabolic effects of interventions to increase exercise in adults with type 2 diabetes. Diabetologia 50:913–921

8. Davies MJ, Heller S, Skinner TC et al (2008) Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. BMJ 336:491–495
9. Christian JG, Bessesen DH, Byers TE, Christian KK, Goldstein MG, Bock BC (2008) Clinic-based support to help overweight patients with type 2 diabetes increase physical activity and lose weight. Arch Intern Med 168:141–146
10. Herder C, Peltonen M, Koenig W et al (2009) Anti-inflammatory effect of lifestyle changes in the Finnish Diabetes Prevention Study. Diabetologia 52:433–442
11. Norris SL, Lau J, Smith SJ, Schmid CH, Engelgau MM (2002) Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. Diabetes Care 25:1159–1171
12. Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N (2003) The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation. Health Technol Assess 7(iii):1–190
13. Li G, Zhang P, Wang J et al (2008) The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet 371:1783–1789
14. Uusitupa M, Peltonen M, Lindstrom J et al (2009) Ten-year mortality and cardiovascular morbidity in the Finnish Diabetes Prevention Study—secondary analysis of the randomized trial. PLoS ONE 4:e5656
15. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 348:383–393
16. Gaede P, Lund-Andersen H, Parving HH, Pedersen O (2008) Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 358:580–591
17. Sone H, Yoshimura Y, Ito H, Ohashi Y, Yamada N (2004) Energy intake and obesity in Japanese patients with type 2 diabetes. Lancet 363:248–249
18. Sone H, Mizuno S, Fujii H et al (2005) Is the diagnosis of metabolic syndrome useful for predicting cardiovascular disease in Asian diabetic patients? Analysis from the Japan Diabetes Complications Study. Diabetes Care 28:1463–1471
19. Sone H, Tanaka S, Ishibashi S et al (2006) The new worldwide definition of metabolic syndrome is not a better diagnostic predictor of cardiovascular disease in Japanese diabetic patients than the existing definitions: additional analysis from the Japan Diabetes Complications Study. Diabetes Care 29:145–147
20. Sone H, Tanaka S, Iimuro S et al (2009) Waist circumference as a cardiovascular and metabolic risk in Japanese patients with type 2 diabetes. Obesity 17:585–592
21. Sone H, Katagiri A, Ishibashi S et al (2002) Effects of lifestyle modifications on patients with type 2 diabetes: the Japan Diabetes Complications Study (JDCS) study design, baseline analysis and three year-interim report. Horm Metab Res 34:509–515
22. Chodosh J, Morton SC, Mojica W et al (2005) Meta-analysis: chronic disease self-management programs for older adults. Ann Intern Med 143:427–438
23. Shojania KG, Ranji SR, McDonald KM et al (2006) Effects of quality improvement strategies for type 2 diabetes on glycemic control: a meta-regression analysis. JAMA 296:427–440
24. The Japan Diabetes Society (2002) Food exchange lists dietary guidance for persons with diabetes. Bunkodo, Tokyo
25. Shikoku University Nutrition Data Base. http://www2-eiyoashi koku-uacjp/ (in Japanese), accessed 1 Sep 2009
26. Ministry of Education C, Sports, Science and Technology, Japan (2004) Standard Tables of Food Composition in Japan. http://wwwmextgojp/b_menu/shingi/gijyutu/gijyutu3/toushin/05031802htm (in Japanese), accessed 1 Sep 2009
27. Baecke JA, Burema J, Frijters JE (1982) A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 36:936–942
28. Klein S, Sheard NF, Pi-Sunyer X et al (2004) Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. Diabetes Care 27: 2067–2073
29. Buse JB, Ginsberg HN, Bakris GL et al (2007) Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 30:162–172
30. The United Kingdom Prospective Diabetes Study Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352:837–853
31. Myint PK, Luben RN, Wareham NJ, Bingham SA, Khaw K-T (2009) Combined effect of health behaviours and risk of first ever stroke in 20, 040 men and women over 11 years' follow-up in Norfolk cohort of European Prospective Investigation of Cancer (EPIC Norfolk): prospective population study. BMJ. doi:10.1136/bmj.b349
32. Nathan DM, Cleary PA, Backlund JY et al (2005) Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 353:2643–2653
33. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 359:1577–1589
34. Araki A, Murotani Y, Kamimiya F, Ito H (2004) Low well-being is an independent predictor for stroke in elderly patients with diabetes mellitus. J Am Geriatr Soc 52:205–210
35. Roumen C, Corpeleijn E, Feskens EJ, Mensink M, Saris WH, Blaak EE (2008) Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabet Med 25:597–605
36. Nothlings U, Schulze MB, Weikert C et al (2008) Intake of vegetables, legumes, and fruit, and risk for all-cause, cardiovascular, and cancer mortality in a European diabetic population. J Nutr 138:775–781
37. Wu JY, Leung WY, Chang S et al (2006) Effectiveness of telephone counselling by a pharmacist in reducing mortality in patients receiving polypharmacy: randomised controlled trial. BMJ 333:522–525
38. Piette JD, Weinberger M, McPhee SJ, Mah CA, Kraemer FB, Crapo LM (2000) Do automated calls with nurse follow-up improve self-care and glycemic control among vulnerable patients with diabetes? Am J Med 108:20–27
39. Piette JD, Weinberger M, Kraemer FB, McPhee SJ (2001) Impact of automated calls with nurse follow-up on diabetes treatment outcomes in a Department of Veterans Affairs Health Care System: a randomized controlled trial. Diabetes Care 24:202–208
40. Lorig K, Ritter PL, Villa F, Piette JD (2008) Spanish diabetes self-management with and without automated telephone reinforcement: two randomized trials. Diabetes Care 31:408–414
41. Maljanian R, Grey N, Staff I, Conroy L (2005) Intensive telephone follow-up to a hospital-based disease management model for patients with diabetes mellitus. Dis Manag 8:15–25

42. Song KH, Ko SH, Kim HW et al (2005) Prospective study of lipoprotein(a) as a risk factor for deteriorating renal function in type 2 diabetic patients with overt proteinuria. Diabetes Care 28:1718–1723
43. Tseng CH (2004) Lipoprotein(a) is an independent risk factor for peripheral arterial disease in Chinese type 2 diabetic patients in Taiwan. Diabetes Care 27:517–521
44. Hiraga T, Kobayashi T, Okubo M et al (1995) Prospective study of lipoprotein(a) as a risk factor for atherosclerotic cardiovascular disease in patients with diabetes. Diabetes Care 18:241–244
45. Murase T, Okubo M, Amemiya-Kudo M, Ebara T, Mori Y (2008) Impact of elevated serum lipoprotein (a) concentrations on the risk of coronary heart disease in patients with type 2 diabetes mellitus. Metabolism 57:791–795
46. Hernandez C, Francisco G, Chacon P, Simo R (2005) Lipoprotein(a) as a risk factor for cardiovascular mortality in type 2 diabetic patients: a 10-year follow-up study. Diabetes Care 28:931–933
47. Kollerits B, Auinger M, Reisig V et al (2006) Lipoprotein(a) as a predictor of cardiovascular disease in a prospectively followed cohort of patients with type 1 diabetes. Diabetes Care 29:1661–1663
48. Scanu AM, Lawn RM, Berg K (1991) Lipoprotein(a) and atherosclerosis. Ann Intern Med 115:209–218
49. Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N (2003) Obesity and type 2 diabetes in Japanese patients. Lancet 361:85

Original Article

Components of Metabolic Syndrome and their Combinations as Predictors of Cardiovascular Disease in Japanese Patients with Type 2 Diabetes. Implications for Improved Definition. Analysis from Japan Diabetes Complications Study (JDCS)

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Aim: The prognostic power of metabolic syndrome (MetS) in patients with diabetes has been studied with inconsistent results depending on the definition of MetS. To clarify the best combination of MetS components to predict future cardiovascular disease (CVD) events, we estimated CVD risk in Japanese patients with type 2 diabetes according to MetS components.
Methods: Patients were categorized according to the presence three MetS components in addition to hyperglycemia. hypertension, dyslipidemia and excess waist circumference (WC) (according to either Japanese or Asian cut-off values). Hazard ratios for CVD events were compared in patients with various categories of MetS components.
Results: At least two components of MetS were required for a significantly elevated risk for CVD; however, component combinations with significantly increased risk differed depending on gender or the WC cut-off value. Any two among 1) excess WC (men ≥90 cm, women ≥80 cm); 2) hypertension (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or use of an antihypertensive agent); and 3) dyslipidemia (triglycerides ≥150 mg/dL or HDL-cholesterol <40 mg/dL or use of drug treatment) could be used to identify significantly higher risk (approximately twice) for CVD regardless of gender.
Conclusions: The results suggest that the current MetS criteria should be modified when applied to patients with type 2 diabetes.

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Key words; Diabetic macroangiopathy, Cardiovascular risk factors, Hypertension, Dyslipidemia

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Introduction

Patients with diabetes are at greater risk for cardiovascular disease (CVD) than non-diabetic subjects, and metabolic syndrome (MetS), a constellation of multiple cardiometabolic risk factors, is strongly asso-

ciated with increased risk of CVD events; however, previously, we found that the diagnosis of MetS had only a limited prognostic value for future CVD events in Japanese patients with type 2 diabetes[1-3]. Since that time many reports have also addressed the issue of whether a diagnosis of MetS is predictive in patients with diabetes, reflecting the need to identify diabetic patients at very high risk for CVD events in clinical settings; unfortunately, the results have been inconsistent[4-13]. Some studies[5-7, 10] revealed that the clinical relevance of a diagnosis of MetS as a predictor of CVD morbidity and mortality differs markedly among diabetic patients, depending on the definition of MetS. Moreover, the contribution of each MetS component to cardiovascular risk was shown to significantly vary in the general population[14].

These findings strongly suggest that various combinations of individual components of MetS could have substantially different contributions to CVD risk in diabetic patients. In fact, a recent cross-sectional study of 4020 German patients with type 2 diabetes[15] demonstrated considerably diverse odds ratios for established CVD according to heterogeneous clusters of traits; however, prospective studies evaluating the impact of specific combinations of MetS components on CVD risk in diabetic populations are scarce, although such a study in the general population has been published recently[16]. Such information would be useful for screening patients at extremely high risk of CVD as well as for improving the definition of MetS for a diabetic subgroup. For this purpose, we determined the prevalence of various combinations of MetS components among Japanese patients with type 2 diabetes and estimated the risks of CVD presented by these components in this patient group.

Methods

The Japan Diabetes Complications Study (JDCS) is a nationwide multi-center prospective study of type 2 diabetic patients[17]. In 1996, 2205 patients aged 40–70 years with previously diagnosed type 2 diabetes but no CVD were registered. The detailed protocol of the JDCS has been described previously[17]. Of the 2205 patients, 1424 (771 men and 653 women, mean age; 58.4±7.4 years) with a complete set of data, including the parameters necessary to satisfy the World Health Organization (WHO)[18] and the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII)[19] criteria for the definition of MetS at baseline, were prospectively followed for 8 years for fatal/non-fatal coronary heart disease (CHD) and stroke events. CHD events consisted of angina pectoris and fatal/non-fatal acute myocardial infarction. A detailed definition of CHD and stroke events was previously described[1]. CHD and stroke events (hereafter referred to as CVD) identified during follow-up were confirmed by at least two members of the experts committee who were blinded as to risk factor status and the other member's diagnosis. The JDCS protocol was conducted according to the Declaration of Helsinki and received approval from the institutional review board. All participants gave written informed consent.

Thresholds for individual risk factors were adopted from the Japanese definition of MetS[20], which is similar to that of IDF[21] with the exception that hypertriglyceridemia and low HDL-cholesterolemia are combined as one component, i.e, 'dyslipidemia'. Since all subjects in this study had diabetes mellitus, 3 criteria other than an elevated fasting plasma glucose level (>110 mg/dL) were used: (i) excess WC (male ≥85 cm, female ≥90 cm), (ii) hypertension (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg), and (iii) dyslipidemia (triglyceride >150 mg/dL and/or HDL-cholesterol <40 mg/dL). MetS is defined as the presence of excess WC and two of the following three parameters: hypertension, dyslipidemia and elevated fasting plasma glucose[20]. Subjects using agents for hypertension or hyperlipidemia were considered to have either hypertension or hyperlipidemia according to the recent MetS criteria[19, 21]. The alternative WC cut-off values for general Asians, as decided by the WHO and the International Diabetes Federation (IDF) definition (male ≥90 cm, female ≥80 cm)[19, 21], were used for additional evaluation.

Data are presented as the means ± SD or as a proportion unless otherwise specified. WC in each group was assessed by Wilcoxon's rank sum test. Cox regression analysis was used to calculate the age-adjusted hazard ratio and 95% confidence intervals (CI) of risk factors for CVD. The SAS software package (Version 9.0, Cary, NC) was used for all analyses. $P<0.05$ was considered significant.

Results

Distribution of Patients According to Status of Risk Factor Clustering

Baseline characteristics of the study patients are shown in **Table 1**. Distribution of patients categorized by risk factor status employing either the Japanese or Asian WC cut-off is shown in **Fig. 1**. Approximately 60–70%, 30–0% or 20–25% of all diabetic patients, including both males and females, had hypertension,

Table 1. Baseline characteristics of patients analyzed

	Men	Women
Number of Patients (%)	771	653
Age (y)	58.2±7.4	58.7±7.4
Diabetes duration (y)	10.9±7.6	10.1±6.7
BMI (kg/m^2)	22.9±2.6	23.4±3.3
Waist circumference (cm)	82.3±7.7	76.5±9.8
Waist/Hip ratio	0.89±0.07	0.83±0.08
Blood pressure (mmHg)	132±16/78±10	132±17/76±10
HbA$_{1c}$ (%)	7.61±1.36	8.05±1.45
Fasting plasma glucose* (mmol/L)	8.3 (7.2, 10.0)	8.6 (7.3, 10.2)
Fasting plasma insulin* (pmol/L)#	6.2 (0.5, 1.9)	7.1 (0.5, 1.9)
Serum LDL cholesterol (mmol/L)	3.03±0.86	3.38±0.82
Serum HDL cholesterol (mmol/L)	1.34±0.39	1.47±0.44
Serum triglycerides** (mmol/L)	1.39 (0.75)	1.29 (0.72)
Current smoker (%)	43.9	8.7
OHA (without insulin) use (%)	72	77
Insulin (with or without OHA) use (%)	16	20
Medication for hypertension (%)	22	29
Medication for hyperlipidemia (%)	15	35

mean ± SD, *median (IQR) or **geometric mean (1SD), #patients on insulin therapy were excluded
OHA, oral hypoglycemic reagents

dyslipidemia or both, respectively. When the Japanese WC cut-off value (male ≥85 cm, female ≥90 cm) was applied, the proportion of female patients with excess WC was much lower than that of male patients. Among all diabetic patients, the proportion of patients having all 3 risk factors (i.e. excess WC, hypertension and dyslipidemia) was 13% among men but only 3% among women. When the Asian WC cut-off value (male ≥90 cm, female ≥80 cm) was used instead of the Japanese cut-off value, the proportion of female patients with excess WC increased nearly 4 times (approx. from 10 to 37%) while the proportion of male patients decreased by half (approx. from 37 to 18%).

CVD Risk of Patients in Individual and Combined Risk Category

Table 2 shows hazard ratios for CVD (i.e. CHD and/or stroke) events in patients in the individual and combined risk categories indicated in **Fig. 1** compared to those not in these areas. For example, patients in area (b+c) were compared to patients in other areas. Analysis was performed using either Japanese or Asian WC cut-off values. In general, especially in female patients, substantially greater risk assessment accuracy was achieved when using the Asian WC cut-off value than the Japanese valve, since a relatively large number of categories with significantly elevated hazard ratios were obtained when the Asian cut-off value was used. Moreover, hazard ratio values were generally higher when using the Asian WC cut-off value.

When the risk for patients included in an individual category (i.e., a b, c, d, e, f, or g) was calculated separately from risks for patients not included in that particular area, male patients with all three MetS components (i.e. area c) had a significantly increased risk, regardless of the WC threshold. Male patients in area f also had a significantly elevated risk, but only when the Asian WC cut-off value was applied; however, in female patients, none of the individual categories represented a significantly increased risk.

When risks in male patients included in combinations of two areas (i.e., (b+c), (c+d) or (c+f)) were assessed and compared with those not included in such combinations of those areas, only men in areas (c+d) and (c+f) had a significantly elevated hazard ratio.

Similarly, when men in areas (b+c+d), (b+c+f) or (c+d+f) were assessed against those in the complement set of each area, men in areas (b+c+f) and (c+d+f) had a significantly elevated risk. In female patients, a substantially different risk profile was obtained in combinations of two or three areas. For example, the hazard ratios for categories (b+c), (b+c+d) and (b+c+f) were significantly elevated to approximately twice that in those in the comple-

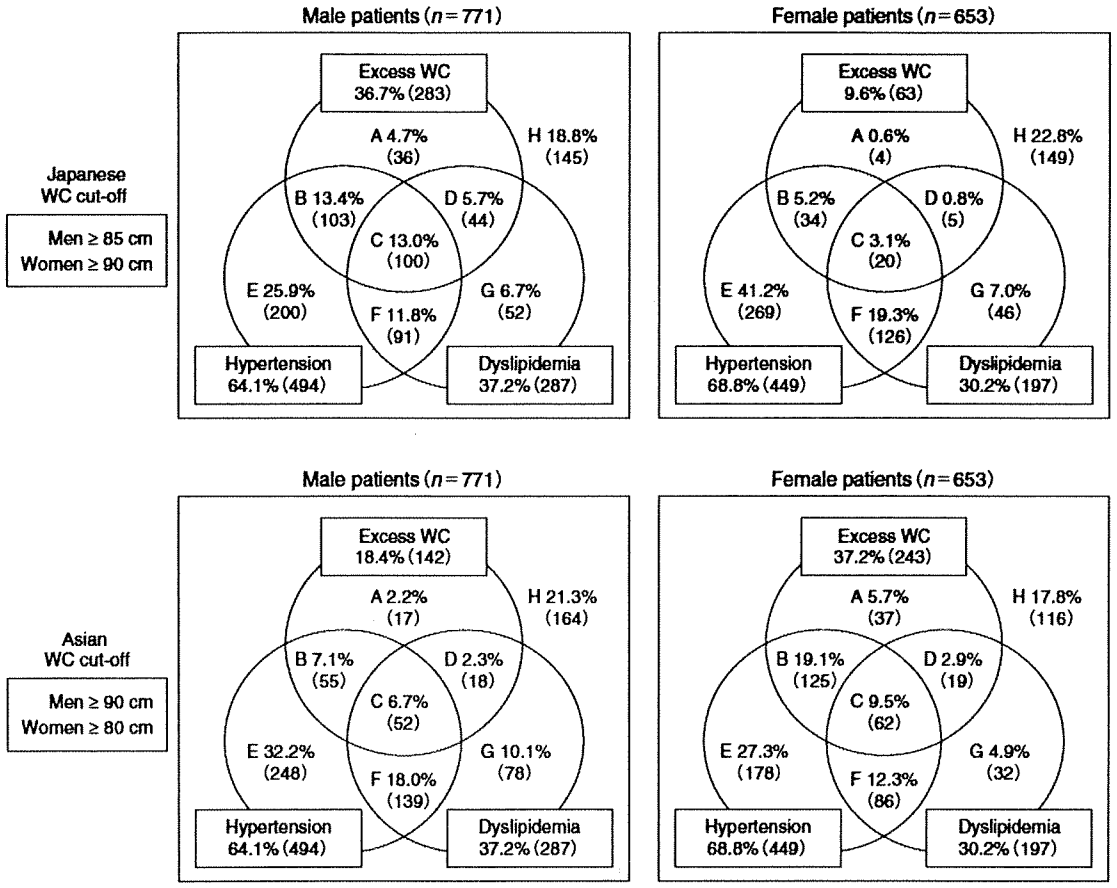

Fig. 1. Distribution of Japanese patients with type 2 diabetes categorized by baseline status of risk factor(s) (excess waist circumference (WC), hypertension and dyslipidemia).

ment set of each area. The current Japanese criteria of MetS[20] (corresponding to patients in area (b+c+d)) were predictive of CVD events only in female patients when the Asian WC cut-off value was applied.

When risks in patients included in a combination of four areas (b+c+d+f) were assessed, both male and female patients had significantly elevated hazard ratios when using the Asian cut-off value. The hazard ratio values were similar to those with combinations of two or three areas.

Discussion

The present analysis prospectively demonstrated in Japanese patients with type 2 diabetes that 1) at least two components of MetS in addition to hyperglycemia are required to have a significantly elevated CVD risk; 2) the combination of MetS components associated with a significantly elevated CVD risk is markedly different depending on gender and the WC cut-off value and 3) the combinations of MetS components with high hazard ratios for CVD did not completely agree with the current definitions of MetS. These findings imply that the current MetS criteria need to be modified when applied to patients with type 2 diabetes.

Although the clinical relevance in diagnosing MetS in diabetic subjects is still under debate[22], a simple assessment tool for cardiovascular risk in patients with diabetes but without an elevated LDL cholesterol level or who do not smoke is greatly needed in clinical settings, as demonstrated by the numerous recent studies that compared the hazard ratio for CVD between diabetic patients with and without MetS[1, 2, 4-13]; unfortunately, the results were inconsistent.

Some of these studies concluded that MetS diagnosed by the current definitions has a considerable role in the increased CVD risk in patients with type 2 diabetes[5, 6, 9, 12, 13], and that the impact of diabetes itself on CVD risk is relatively limited without coex-

Table 2. Hazard ratio of CVD events (CHD and/or stroke) in diabetic patients according to individual and combined risk categories indicated in Fig. 1 compared to those not in these categories

Threshold	Japanese cut-off value				Asian cut-off value			
	Men ≥85 cm		Women ≥90 cm		Men ≥90 cm		Women ≥80 cm	
Patient category	Hazard ratio (95% C.I.)	*p* value[§]	Hazard ratio (95% C.I.)	*p* value[§]	Hazard ratio (95% C.I.)	*p* value[§]	Hazard ratio (95% C.I.)	*p* value[§]
a	0.54 (0.13–2.21)	0.39	n/a[¶]		n/a[¶]		n/a[¶]	
b	0.68 (0.31–1.48)	0.33	2.27 (0.90–5.75)	0.08	0.94 (0.38–2.33)	0.89	1.71 (0.90–3.26)	0.10
c	2.05 (1.18–3.57)	0.01	n/a[¶]		2.25 (1.12–4.54)	0.02	1.91 (0.85–4.28)	0.12
d	1.39 (0.56–3.45)	0.48	n/a[¶]		1.33 (0.33–5.42)	0.69	1.88 (0.46–7.78)	0.38
e	0.80 (0.46–1.39)	0.43	0.74 (0.40–1.36)	0.34	0.69 (0.40–1.17)	0.17	0.54 (0.25–1.15)	0.11
f	1.64 (0.88–3.05)	0.12	1.90 (1.00–3.61)	0.05	1.73 (1.03–2.93)	0.04	1.11 (0.47–2.61)	0.82
g	0.61 (0.19–1.94)	0.40	1.65 (0.65–4.17)	0.29	0.85 (0.37–1.97)	0.71	1.27 (0.39–4.10)	0.69
b+c	1.34 (0.82–2.20)	0.24	1.33 (0.52–3.37)	0.55	1.57 (0.88–2.82)	0.13	2.06 (1.14–3.71)	0.02
c+d	1.97 (1.18–3.27)	0.01	–	0.99	2.06 (1.08–3.91)	0.03	1.98 (0.95–4.11)	0.07
c+f	2.12 (1.32–3.41)	0.00	1.53 (0.80–2.91)	0.20	2.12 (1.32–3.41)	0.00	1.53 (0.80–2.91)	0.20
b+c+d*	1.42 (0.88–2.28)	0.15	1.22 (0.48–3.09)	0.67	1.57 (0.90–2.73)	0.11	2.19 (1.22–3.93)	0.01
b+c+f	1.63 (1.03–2.58)	0.04	1.87 (1.03–3.40)	0.04	1.93 (1.22–3.07)	0.01	2.04 (1.13–3.68)	0.02
c+d+f	2.16 (1.36–3.43)	0.00	1.47 (0.77–2.79)	0.24	2.12 (1.33–3.39)	0.00	1.63 (0.88–3.04)	0.12
b+c+d+f	1.74 (1.01–2.77)	0.02	1.81 (1.00–3.29)	0.05	1.96 (1.23–3.11)	0.00	2.22 (1.21–4.05)	0.01

e.g., patients in area (b + c) were compared to patients in an area other than (b + c).
*corresponds to Japanese criteria of metabolic syndrome, [§]ANOVA, [¶]could not calculate because of no events

isting MetS or its components[23]. In contrast, in Finnish women[11] and Singaporean men[24], MetS diagnosed by existing criteria does not present a further risk of CVD in addition to that presented by type 2 diabetes per se. Likewise, combinations of any two MetS components were not significantly associated with higher mortality in Italian patients with type 2 diabetes[7, 25] and a single component of MetS was a more powerful predictor than the overall syndrome in Type 1 diabetic patients[26]. Similarly, a recent report of the United Kingdom Prospective Diabetes Study[4] also questioned the clinical value of diagnosing MetS for CVD risk stratification in patients newly diagnosed with type 2 diabetes.

These inconsistencies in previous prospective studies along with our current results suggest that the established definitions of MetS leave room for improvement when applied to diabetic patients. It also implies that specific combinations of MetS components that increase CVD risk in diabetic patients differ depending on the ethnic group; therefore, an ethnicity-specific definition of MetS might be necessary.

The current results also revealed gender differences in combinations of MetS components associated with higher CVD risks. In male patients, dyslipidemia had a relatively large prognostic value since area [c + (d and/or f)] indicated a significantly elevated risk for CVD events. On the other hand, in female patients, hypertension was important, which was similar to the result reported in Chinese patients with type 2 diabetes[10]. A large gender difference was also seen in other cohorts[11, 24, 27]. Most studies did not stratify results by gender in their analysis, which is considered to be a of the low prognostic power of the established definition of MetS; however, the gender difference became insignificant when area (b + c + d + f) in **Fig. 1** is considered.

The current results also indicated that the Asian WC cut-off value is more appropriate than the Japanese cut-off value, even for Japanese diabetic patients, for discriminating patients at high risk; however, WC per se was not indispensable for predicting CVD events in our patients despite the worldwide definition of IDF[21] as well as Japanese[20] definitions of MetS, as we reported previously[2]. The poor prognostic power of the IDF definition in diabetic subjects has also been reported for other ethnic groups, such as Hong Kong Chinese[5], Native Americans[6] and Italians[7]. Lack of a rationale for excess WC as a mandatory component of MetS was also shown in recent studies of non-diabetic subjects[14, 28].

Table 3 shows the suggested definitions of MetS for Japanese patients with type 2 diabetes based on our current and previous results. This criteria is similar

Table 3. Suggested definition of MetS for Japanese patients with type 2 diabetes for predicting future CVD events

Patients with two or more of the following
1) Excess WC: men ≥90 cm, women ≥80 cm
2) Hypertension: systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg or use of an agent for this condition
3) Dyslipidemia: triglyceride ≥150 mg/dL and/or HDL-cholesterol <40 mg/dL or use of an agent for this condition

to that of the American Heart Association/National Heart Lung and Blood Institute (AHA/NHLBI)[19] (revised version of NCEP-ATPIII) but differs in terms of dyslipidemia. that is, an elevated triglyceride level and decreased HDL cholesterol level were treated as individual components in the AHA/NHLBI definition. We previously determined that hazard ratios of hypertriglyceridemia alone and hypertriglyceridemia or low HDL cholesterol were almost identical, but the latter covers more patients. These two indices are known to be frequently correlated and so could have greater prognostic power when combined.

Monami and colleagues[8] suggested that a MetS diagnosis based only on the unweighted number of components present in each patient, without considering each specific combination, could be inadequate to predict the risk level because a different risk profile is determined by different combinations of metabolic alterations. Although our current results principally support their conclusion, we still consider that using area (b+c+d+f) in **Fig. 1** as a definition of MetS has merit in clinical settings because 1) the hazard ratios are similar (or even higher in female patients) to other significant combinations, 2) it can be used regardless of patient gender, 3) it covers more subjects than combinations of two or three areas among b, c, d and f, and 4) it is simple and easy to remember.

The current study has several strengths and limitations. The strengths include the nationwide multicentered setting and prospective design, which enabled us to assess the predictability of a CVD event. In addition, all institutes that participated are university or large general hospitals; therefore, the quality of risk evaluation and the accuracy of CVD diagnosis were excellent. A limitation is that the results may only be applicable to Japanese patients with type 2 diabetes. As described above, ethnicity can be considered an important factor for determining CVD risk in diabetic subjects as well as in the general population, so the clinical significance of MetS should be determined separately in each ethnic group. In addition, we do not have sufficient data on mortality, which needs to be determined in the future. We did not determine different cut-off values for blood pressure and serum lipids since their cut-off values have been well-established in many guidelines, unlike WC.

In conclusion, Japanese diabetic patients with two or more features of MetS with excess WC according to the Asian cut-off value (male ≥90 cm, female ≥80 cm), hypertension and dyslipidemia have a significantly elevated CVD event risk. Nevertheless, the rationale was weak for including WC as a mandatory component when evaluating CVD risk despite existing definitions of MetS. The definition of MetS should be modified to provide better prognostic value in clinical settings of diabetes management.

Appendix

The Japan Diabetes Complications Study (JDCS) Group:

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References

1) Sone H, Mizuno S, Fujii H, Yoshimura Y, Yamasaki Y, Ishibashi S, Katayama S, Saito Y, Ito H, Ohashi Y, Akanuma Y, Yamada N: Japan Diabetes Complications Study: Is the diagnosis of metabolic syndrome useful for predicting cardiovascular disease in asian diabetic patients? Analysis from the Japan Diabetes Complications Study. Diabetes Care, 2005; 28:1463-1471
2) Sone H, Tanaka S, Ishibashi S, Yamasaki Y, Oikawa S, Ito H, Saito Y, Ohashi Y, Akanuma Y, Yamada N: The new worldwide definition of metabolic syndrome is not a better diagnostic predictor of cardiovascular disease in Japanese diabetic patients than the existing definitions: additional analysis from the Japan Diabetes Complications Study. Diabetes Care, 2006; 29:145-147
3) Sone H, Tanaka S, Ishibashi S, Yamasaki Y, Oikawa S, Ito H, Saito Y, Ohashi Y, Akanuma Y, Yamada N; Japan Diabetes Comlications Study (JDCS) Group: The new worldwide definition of Metabolic syndrome is not a better diagnostic predictor of cardiovascular disease in Japanese diabetic patients than the existing definitional analysis from the Japan Diabetes Complications Study. Diabetes Care, 2006; 29:145-147
4) Cull CA, Jensen CC, Retnakaran R, Holman RR: Impact of the metabolic syndrome on macrovascular and microvascular outcomes in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study 78. Circulation, 2007; 116:2119-2126
5) Tong PC, Kong AP, So WY, Yang X, Ho CS, Ma RC, Ozaki R, Chow CC, Lam CW, Chan JC, Cockram CS: The usefulness of the International Diabetes Federation and the National Cholesterol Education Program's Adult Treatment Panel III definitions of the metabolic syndrome in predicting coronary heart disease in subjects with type 2 diabetes. Diabetes Care, 2007; 30:1206-1211
6) de Simone G, Devereux RB, Chinali M, Best LG, Lee ET, Galloway JM, Resnick HE: Prognostic impact of metabolic syndrome by different definitions in a population with high prevalence of obesity and diabetes: the Strong Heart Study. Diabetes Care, 2007; 30:1851-1856
7) Monami M, Marchionni N, Masotti G, Mannucci E: IDF and ATP-III definitions of metabolic syndrome in the prediction of all-cause mortality in type 2 diabetic patients. Diabetes Obes Metab, 2007; 9:350-353
8) Monami M, Lambertucci L, Ungar A, Pieri M, Masotti G, Marchionni N, Mannucci E: Is the third component of metabolic syndrome really predictive of outcomes in type 2 diabetic patients? Diabetes Care, 2006; 29:2515-2517
9) Hillier TA, Rizzo JH, Pedula KL, Cauley JA, Schwartz AV, Ensrud KE, Browner WS: Increased mortality associ-

ated with the metabolic syndrome in older women with diabetes. Diabetes Care, 2005; 28:2258-2260
10) Ko GT, So WY, Chan NN, Chan WB, Tong PC, Li J, Yeung V, Chow CC, Ozaki R, Ma RC, Cockram CS, Chan JC: Prediction of cardiovascular and total mortality in Chinese type 2 diabetic patients by the WHO definition for the metabolic syndrome. Diabetes Obes Metab, 2006; 8:94-104
11) Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M: Proteinuria and metabolic syndrome as predictors of cardiovascular death in non-diabetic and type 2 diabetic men and women. Diabetologia, 2006; 49:56-65
12) Najarian RM, Sullivan LM, Kannel WB, Wilson PW, D'Agostino RB, Wolf PA: Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring Study. Arch Intern Med, 2006; 166:106-111
13) Guzder RN, Gatling W, Mullee MA, Byrne CD: Impact of metabolic syndrome criteria on cardiovascular disease risk in people with newly diagnosed type 2 diabetes. Diabetologia, 2006; 49:49-55
14) Mancia G, Bombelli M, Corrao G, Facchetti R, Madotto F, Giannattasio C, Trevano FQ, Grassi G, Zanchetti A, Sega R: Metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study: daily life blood pressure, cardiac damage, and prognosis. Hypertension, 2007; 49:40-47
15) Hanefeld M, Koehler C, Gallo S, Benke I, Ott P: Impact of the individual components of the metabolic syndrome and their different combinations on the prevalence of atherosclerotic vascular disease in type 2 diabetes: the Diabetes in Germany (DIG) study. Cardiovasc Diabetol, 2007; 26:6-13
16) Guize L, Thomas F, Pannier B, Bean K, Jego B, Benetos A: All-cause mortality associated with specific combinations of the metabolic syndrome according to recent definitions. Diabetes Care, 2007; 30:2381-2387
17) Sone H, Katagiri A, Ishibashi S, Abe R, Saito Y, Murase T, Yamashita H, Yajima Y, Ito H, Ohashi Y, Akanuma Y, Yamada N; JD Study Group: Effects of lifestyle modifications on patients with type 2 diabetes: the Japan Diabetes Complications Study (JDCS) study design, baseline analysis and three year-interim report. Horm Metab Res, 2002; 34:509-515
18) Organization WH: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Genova, Switzerland: Department of non-communicable Disease Surveillance; 1999,
19) Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation, 2005; 112:2735-2752
20) Definition and the diagnostic standard for metabolic syndrome--Committee to Evaluate Diagnostic Standards for Metabolic Syndrome. Nippon Naika Gakkai Zasshi, 2005; 94:794-809
21) Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group: The metabolic syndrome--a new worldwide definition. Lancet, 2005; 366:1059-1062
22) Fujita T: The metabolic syndrome in Japan. Nature Clinical Practice, 2008; 5 Suppl 1:S15-18
23) Liu J, Grundy SM, Wang W, Smith SC Jr, Vega GL, Wu Z, Zeng Z, Wang W, Zhao D: Ten-year risk of cardiovascular incidence related to diabetes, prediabetes, and the metabolic syndrome. Am Heart J, 2007; 153:552-558
24) Mak KH, Ma S, Heng D, Tan CE, Tai ES, Topol EJ, Chew SK: Impact of sex, metabolic syndrome, and diabetes mellitus on cardiovascular events. Am J Cardiol, 2007; 100:227-233
25) Bruno G, Merletti F, Biggeri A, Bargero G, Ferrero S, Runzo C, Prina Cerai S, Pagano G, Cavallo-Perin P; Casale Monferrato Study: Metabolic syndrome as a predictor of all-cause and cardiovascular mortality in type 2 diabetes: the Casale Monferrato Study. Diabetes Care, 2004; 27:2689-2694
26) Pambianco G, Costacou T, Orchard TJ: The prediction of major outcomes of type 1 diabetes: a 12-year prospective evaluation of three separate definitions of the metabolic syndrome and their components and estimated glucose disposal rate: the Pittsburgh Epidemiology of Diabetes Complications Study experience. Diabetes Care, 2007; 30:1248-1254
27) Hunt KJ, Williams K, Hazuda HP, Stern MP, Haffner SM: The metabolic syndrome and the impact of diabetes on coronary heart disease mortality in women and men: the San Antonio Heart Study. Annals of Epidemiology, 2007; 17:870-877
28) Lee J, Ma S, Heng D, Tan CE, Chew SK, Hughes K, Tai ES: Should central obesity be an optional or essential component of the metabolic syndrome? Ischemic heart disease risk in the Singapore Cardiovascular Cohort Study. Diabetes Care, 2007; 30:343-347

Association Between Serum Uric Acid and Development of Type 2 Diabetes

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OBJECTIVE — To systematically evaluate the association between serum uric acid (SUA) level and subsequent development of type 2 diabetes.

RESEARCH DESIGN AND METHODS — We searched Medline (31 March from 1966 to 2009) and Embase (31 March from 1980 to 2009) for observational cohort studies examining the association between SUA and the risk of type 2 diabetes by manual literature search. Relative risks (RRs) for each 1 mg/dl increase in SUA were pooled by using a random-effects model. The studies included were stratified into subgroups representing different study characteristics, and meta-regression analyses were performed to investigate the effect of these characteristics on the association between SUA level and type 2 diabetes risk.

RESULTS — The search yielded 11 cohort studies (42,834 participants) that reported 3,305 incident cases of type 2 diabetes during follow-up periods ranging from 2.0 to 13.5 years. The pooled RR of a 1 mg/dl increase in SUA was 1.17 (95% CI 1.09–1.25). Study results were consistently significant (i.e., >1) across characteristics of participants and study design. Publication bias was both visually and statistically suggested ($P = 0.03$ for Egger's test, 0.06). Adjustment for publication bias attenuated the pooled RR per mg/dl increase in SUA (RR 1.11 [95% CI 1.03–1.20]), but the association remained statistically significant ($P = 0.009$).

CONCLUSIONS — The current meta-analysis suggests that SUA level is positively associated with the development of type 2 diabetes regardless of various study characteristics. Further research should attempt to determine whether it is effective to utilize SUA level as a predictor of type 2 diabetes for its primary prevention.

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Identifying risk factors for the development of type 2 diabetes is essential for its early screening and prevention. Serum uric acid (SUA) level has been suggested to be associated with risk of type 2 diabetes. Biologically, uric acid (UA) plays an important role in worsening of insulin resistance in animal models by inhibiting the bioavailability of nitric oxide, which is essential for insulin-stimulated glucose uptake (1). However, hyperinsulinemia as a consequence of insulin resistance causes an increase in SUA concentration by both reducing renal UA secretion (2) and accumulating substrates for UA production (3). Therefore, it remains controversial whether SUA is independently associated with the development of type 2 diabetes. The aim of our meta-analysis was to summarize the association between SUA level and risk of type 2 diabetes derived from previously published cohort studies and to examine the effect of study characteristics on this association.

RESEARCH DESIGN AND METHODS

Search strategy

The meta-analysis was fundamentally conducted according to the checklist of the Meta-analysis of Observational Studies in Epidemiology (4). We performed a systematic literature search of Medline (31 March from 1966 to 2009) and Embase (31 March from 1980 to 2009) for observational cohort studies examining the association between SUA level and risk of type 2 diabetes. The key words were related to UA (combined exploded version of the medical subject headings [MeSH] [uric acid] and the following text words: hyperuricemia OR [acid AND uric] OR trioxopurine OR trihydroxypurine OR urate OR gout OR gouts) and type 2 diabetes (combined unexploded version of MeSH [diabetes OR diabetes, type 2] and the following text words [hyperglycemias OR hyperglycemia OR [diabetes mellitus AND [type 2 OR type II OR ketosis resistant OR ketosis-resistant OR maturity onset OR maturity-onset OR noninsulin dependent OR non insulin dependent OR non-insulin-dependent OR slow onset OR slow-onset OR stable OR adult onset OR adult-onset]] OR MODY OR type 2 diabetes).

Included reports had to meet the following criteria: *1*) prospective or historical cohort study, *2*) inclusion of type 2 diabetes as a specified outcome, *3*) baseline assessment of SUA level, and *4*) inclusion of data on relative risk (RR), which is generally expressed as the odds ratio in a historical cohort study or the risk ratio in a prospective cohort study, and its corresponding 95% CIs (or data to calculate them) for type 2 diabetes associated with SUA level. When two or more studies were conducted using the same subjects, the study that included the most recently updated data was selected.

Data abstraction

The data that we abstracted included the first author's name, year of publication, country of origin, cohort design (i.e., prospective or historical cohort), methods for ascertaining diabetes, mean follow-up duration, mean or midpoint of participants' age, proportion of men, baseline SUA level, number of participants and events, and adjusted variables. Odds and risk ratios were combined as indicators of RR, based on the assumption that the odds ratio is an approximation of the risk ratio; this assumption has some limitations, however, especially when the outcome of interest is common (5).

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